Short Stature in Childhood and Adolescence

Part 1: Medical management

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SUMMARY

Childhood short stature is common in family practice. Familial short stature and constitutional growth delay account for most cases, and there are clear guidelines for differentiating these from each other and from less common pathologic conditions. Appropriate investigation, treatment, and referral are delineated, and growth hormone therapy is described. An integrated medical-psychosocial approach to care is recommended.

RÉSUMÉ

Il arrive fréquemment que l'on rencontre des enfants de petite taille en pratique familiale. La plupart des cas trouvent leur explication par la présence d'une famille à petite taille et d'un retard de croissance constitutionnel. Il existe un guide clair pour établir la différence entre ces conditions et d'autres pathologies moins fréquentes. L'article précise l'investigation et le traitement appropriés, le besoin de consultation et décrit la thérapie à l'hormone de croissance. On recommande une approche médico-psychosociale intégrée pour ce type de soins.

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SHORT STATURE IS A COMMON problem in family practice, representing that patient population whose height is more than two standard deviations below the mean, or below the third percentile. Statistically, approximately 80% of these children will have constitutional growth delay or familial short stature (about evenly divided),[1,2] and the remaining 20% have more serious pathologic causes.

Growth charts are the most useful method of monitoring normal growth patterns. Data plotted over time allow the physician to determine whether the child is of normal stature and growing at a normal rate.[3] The postnatal linear growth rate is the greatest in early infancy (with an average growth of 18 cm/y), slows in midchildhood (with a growth range between 5 to 7.5 cm/y), accelerates at puberty, and then decelerates until epiphysial fusion occurs, at which time growth ceases.[4-7]

Fully two thirds of normal infants will shift their linear growth pattern before the age of 18 months.[8] However, by 2 to 3 years of age, children will usually reach a growth chart percentile that will be maintained until puberty. That is, the growth of an individual child will usually progress along the same percentile curve from 2 to 9 years of age.[7,9-11] Abnormal growth is reflected by a deviation from the percentile curve that he or she was following previously. Short stature is defined as height less than the third percentile for age, sex, and ethnic background.[12]

While most of the literature focuses on physical considerations, the psychosocial aspects of short stature can be equally important. The long-term prospects for children who remain significantly short as adults are uncertain; a number of outcome studies suggest poor social and vocational adjustment.[13-17] A physician who offers informed and sensitive support and guidance, in concert with the customary physical examination, investigation, and treatment, is sometimes able to mitigate such disheartening sequelae.

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Determinants of growth

The linear growth and final adult stature of an individual depend on multiple factors. Familial and genetic factors are among the most important influences on growth. The midparental height, which is the average of the heights of each parent, allows predictions of the ultimate height of the child.[18] The midparental height should be adjusted as directed by Tanner et al,[18] by adding

6.5 cm to the midparental height for a boy's chart, and by subtracting 6.5 cm from the midparental height for a girl's chart. The adjusted midparental height thus allows a target for genetic expectation. The correlation of a child's height with this midparental height is 0.5. The correlation of an adult's height with his or her midparental height is 0.7.[19]

Racial factors, obviously genetic, are also important. The difference between blacks and whites in proportion of upper to lower body (U/L ratio) is clinically significant.[20,21] However, the growth rate difference for black and white populations can be considered inconsequential, and a single growth curve can be used.[22] This is not the case for Oriental populations, in which the mean height and weight is less than that of whites.[9] There are also many other influences on final adult height.

It is important not to overlook intrauterine growth and the intrauterine factors that can influence postnatal growth. Insult in the early stages of gestation will often result in intrauterine growth retardation (IUGR): these children can continue to grow poorly after delivery and be short as adults. However, if the insult to growth occurs during the third trimester, compensatory growth is frequently observed in early infancy. Children who have IUGR can be observed to have limited growth in subsequent years.[23] However, infants who are small for gestational age (in weight) but of normal length have normal growth potential.[24] Virtually any factor that can influence intrauterine growth and fetal well-being can be expressed after delivery as short stature.

Environmental factors can also affect growth. Malnutrition or malnourishment, including specific nutrient deficiencies, such as iron or zinc, can result in short stature.[25-27] Malabsorption syndromes, such as celiac disease or cystic fibrosis, can result in short stature by causing malnourishment. Poverty has a role in short stature, more as a reflection of poor nutrition and chronic illness than of psychosocial factors.[28] Chronic illness of virtually any organ system can interfere with linear growth. Most of these cases are associated with low levels of insulin-like growth factor (or somatomedin-C); we do not, however, fully understand the mechanisms involved.[29]

Finally, endocrinologic factors exert profound influences on normal growth during childhood. Thyroid hormone is an essential stimulant for postnatal growth. A deficiency of thyroid hormone can slow linear growth, leading to short stature. Similarly, an excess of glucocorticoids can stunt linear growth. Sex steroids exert their influence on the pubertal growth spurt, and their absence does not usually affect the growth of prepubertal children. Children with precocious puberty or excessive production of androgens will have accelerated growth that can advance bone maturation, leading to premature epiphysial fusion and adult short stature.[30-32] Growth hormone and somatomedins are essential for growth. Growth hormone stimulates the production of somatomedins, which directly stimulate cartilage growth.[33] The exact, relative roles of somatotropin and somatomedins (especially somatomedin-C [SMC/IGF-1]) in influencing growth are not completely understood.[34-36]

Constitutional or familial short stature

Fully 80% of children with short stature will have either constitutional growth delay or familial short stature. It is important to identify these syndromes; the main treatment is reassuring the parents.

Both familial short stature and constitutional growth delay can be regarded as variants of normal, usually reflective of genetic influences and possibly subtle disorders of growth hormone secretion.[37]

A child must meet the following criteria to be considered as having familial short stature[38]:

1. Projected adult height is within 10 cm of midparental height or within 8.5 cm of the adjusted midparental height.
2. Either the parents or other first-degree relatives are short.
3. Bone age is normal and similar to chronological age.
4. Growth is generally maintained along a curve parallel to, but slightly below, the third percentile on growth charts.
5. The remainder of the history, physical examination, and laboratory investigation is normal.

Constitutional growth delay, on the other hand, probably reflects slow skeletal

and pubertal maturation. A typical scenario would be as follows[17,38]:

1. Birth size is normal, and the infant grows normally for some time.
2. Growth and weight gain decelerate for several months, so that both height and weight are below the fifth percentile by the end of infancy (age 2 or 3 years). Growth velocity after age 3 to 5 years is normal.
3. Skeletal maturation slows in a parallel manner; bone age approximately equals the height age, but is delayed for chronological age.
4. Growth occurs parallel to the fifth percentile, and growth velocity stays normal for bone age.
5. Both the appearance of secondary sexual characteristics and the adolescent growth spurt are delayed as a result of the delayed onset of puberty.
6. Final adult height and sexual development are normal.
7. There is often a similar family history of "late bloomers."
8. There are no other historical, physical, or laboratory abnormalities.
9. The midparental height is normal.

Constitutional growth delay occurs more often in boys than in girls.[39]

The ultimate attainable adult height of a child can be predicted from bone age and present height. There are three methods of height prediction, all of comparable accuracy. The most widely used is that developed by Bayley and Pinneau,[40] based on data derived from California children. Two other methods use midparental height in the regression equations for height prediction. The Roche, Wainer, and Thissen (RWT) method[41] was also developed in the United States, while the Tanner and colleagues[42] method was developed in Britain.

Pathologic short stature

Pathologic short stature represents approximately 20% of cases and could reflect one or more of the following influences or diseases:

- intrauterine influences (such as IUGR);
- malnutrition, malabsorption, or psychosocial deprivation;
- chronic systemic disease, such as inflammatory bowel disease or renal tubular acidosis;
- genetic syndromes, such as Down syndrome, trisomies D and E, or Turner syndrome;
- skeletal disorders or dysmorphism; and
- endocrinologic disorders, such as hypothyroidism, glucocorticoid excess, Cushing's disease, disorders of excessive estrogen or testosterone secretion, and growth hormone deficiency.

It is clearly important to identify pathologic causes of short stature, as specific treatment is sometimes available.

Proportionate or disproportionate skeleton? The determination of whether the body habitus of the child is proportionate or disproportionate is important for differential diagnosis.[43,44] Disproportionate short stature suggests skeletal dysplasia or rickets. More than 100 forms of skeletal dysplasia have been identified.[45,46] The measurement of the upper to lower body segments, and of the arm span minus height, is useful in identifying this group. The upper to lower segment ratio is obtained by measuring the height above and below the symphisis pubis. It varies, with a typical mean of approximately 1.7 at birth, 1.3 at 3 years of age, and 1.0 at 7 years of age. Arm span (measured with the arms fully extended) minus height values are about −3 to age 7 years and 0 from age 8 to 12 years. By age 14 years the values are +4 for boys and +1 for girls.[38] Skeletal x-ray examinations can be particularly helpful.

Proportionate short stature can be caused by prenatal influences or postnatal influences.

Prenatal influences. Prenatal influences include any cause of IUGR. Remember that a small infant with normal growth velocity has a good outlook in terms of growth potential.[24] However, any insult that occurs in the first trimester is more likely to result in postnatal short stature than is a third-trimester insult.[3] Chromosomal abnormalities are a clear cause of prenatal proportionate short stature. These chromosomal abnormalities are often recognizable by their physical stigmata. Turner syndrome, which is present in one out of 2000 live births of female infants, accounts for one out of 60 cases of female short stature.[38]

The only indication of Turner syndrome is sometimes short stature. Certainly a karyotype should be performed if this syndrome is suspected.[47] A buccal smear alone is inadequate, because of a high incidence of mosaicism.[48]

Postnatal influences. Postnatal influences that can result in proportionate short stature include endocrine disorders, such as growth hormone deficiency (secondary to hypopituitarism),[49,50] hypothyroidism, and glucocorticoid excess.[51,52] The following signs indicate growth hormone deficiency.

1. Skeletal age is less than chronological age.
2. Skull x-ray films show enlarged sella turcica, sphenoid erosion, or calcifications in the case of a craniopharyngioma.
3. A computed tomographic scan indicates a small sellar volume.[53,54]
4. Growth velocity is less than normal, in the absence of another recognizable cause of linear growth failure.

Specific growth hormone testing is warranted if a growth hormone deficiency is suspected. (This should be left to an experienced endocrinologist.)[12,55]

Hypothyroidism can be suggested strictly on the basis of clinical features. The diagnosis will be confirmed by performing a serum-free thyroxine index. Glucocorticoid excess[51,52] can have, as its only feature, a deceleration of linear growth. It can be confirmed by a 24-hour free cortisol testing or an overnight dexamethasone suppression test.

Malnutrition must be considered as a cause of short stature in the context of excess dieting, low socio-economic status, child abuse, chronic gastrointestinal illness, including inflammatory bowel disease, gluten enteropathy, other causes of chronic diarrhea,[56,57] and anorexia and bulimia nervosa.

Other chronic diseases that can result in proportionate short stature include congenital heart disease, anemia, renal disease, chronic pulmonary disease, and joint disease.[58]

Clinical approach

As with any medical problem, but perhaps even more so, the approach to short stature must involve a thorough medical history, physical examination, and appropriate screening laboratory investigation. Specific tests must then be aimed at suspected illnesses.

The medical history must include such details as the birth weight of the child, the birth length of the child (if known), the gestational age of the baby at birth, and any noted congenital anomalies. Any intrauterine insults or maternal complications, particularly during the first trimester, should be noted. This should include any history of infections, drug use, or placental insufficiency. A complete systems review of the child should be performed in order to screen for symptoms of chronic illness. Family trauma, emotional trauma, and psychosocial status should be assessed. Finally, the family history should be screened, including the heights of the parents and their growth patterns, if available, as well as the heights of other close relatives. The age of menarche and puberty (for example, age of shaving) should be recorded. The family history, as it pertains to any potential inherited or genetic disease, is very important.

Physical examination should initially consist of accurate measurements of both height and weight, correctly plotted on a growth chart. Certainly this is the basis for the diagnosis of short stature. The child should be observed for visual recognition of clues that could lead to the diagnosis of dysmorphic syndromes or specific endocrine disorders. A complete physical examination should be performed, with a determination of the body habitus, beginning with the derivation of the proportion of upper to lower body and the arm span to height value.

Laboratory testing can be divided into screening studies for children without an obvious explanation of short stature and more specific assays when a particular disease or process is suspected. Appropriate screening laboratory investigations would include a complete blood cell count to exclude anemia, leukemia, chronic infection, or malabsorption; an erythrocyte sedimentation rate measurement to screen for chronic inflammation; tests of serum electrolytes, blood urea nitrogen, and creatinine, as well as urinalysis and a urinary pH determination to exclude renal disease; se-

rum calcium, phosphorus, and alkaline phosphatase measurements to rule out rickets; and a serum thyroxine and triiodothyronine resin uptake and thyroid-stimulating hormone assessment to rule out hypothyroidism. Additional investigations can include a karyotype to rule out Turner syndrome. A bone age (x-ray examination of left hand and wrist) will assess the skeletal maturation and assist in predicting the final height.

Finally, consider taking a growth hormone level in children who have no other explainable cause for their short stature and who have the following features:

- abnormal growth velocity (height gain each year is low compared with growth velocity curves for typical girls and boys)[4];
- normal body proportions;
- normal screening test results; and
- delayed skeletal maturation.

Because growth hormone secretion is pulsatile, a single random growth hormone level is of no clinical value. Provocative growth hormone testing in response to clonidine, levodopa, insulin, or arginine (all of which increase growth hormone stimulation) can be performed.[59] Although controversial, the current standard requires that a child show an inadequate response to at least two of these pharmacologic stimuli before the diagnosis of growth hormone deficiency can be made. Because of the difficulty and uncertainty in interpreting these tests, they should be performed by someone with specific expertise, such as a pediatric endocrinologist.

Managing the short stature child

Obviously, accurate diagnosis is of the utmost importance if short stature is to be treated successfully. Fortunately, the parents can be reassured that the child with familial short stature or consitutional growth delay does not have a serious underlying disorder. In particular, the child with constitutional growth delay can be expected to attain a normal adult height. However, the prognosis for the child with pathologic short stature is more uncertain, depending on the underlying cause. Specific treatment for underlying illness will usually result in catch-up growth. Thus, it is very important to treat the hypothyroid child with thyroid hormone replacement, the malnourished child with specific nutritional therapy, and the child who clearly has a growth hormone deficiency with growth hormone.

Human growth hormone (extracted from harvested pituitary glands) has been associated with several cases of Creutzfeldt-Jakob disease and has been withdrawn from the market.[60] Early problems of growth hormone antibody production and allergy side effects associated with the first generation of biosynthetic growth hormone[61] have been resolved by the development of a methionine-free, highly purified recombinant growth hormone.[62] The use of growth hormone-releasing hormone in children with growth hormone deficiency secondary to a hypothalamic defect also shows promise.[63-67] In the future, insulin-like growth factor (somatomedin-C) could be available for treatment of growth hormone deficiency and possibly for the treatment of other causes of short stature.

Growth hormone therapy in children with classic growth hormone deficiency results in an early catch-up growth, particularly in younger children.[68] However, the final adult height is usually less than expected based on the patient's genetic background.[69] This could reflect a suboptimal dose or a suboptimal mode or frequency of growth hormone administration.[70]

Growth hormone therapy for cases other than growth hormone deficiency can also increase growth velocity and result in increased adult height.[71] The optimal dosing, again, is likely the limiting factor in achieving consistent results.[72]

The treatment of very short children with no demonstrated abnormality remains difficult and controversial.[72,73] Some authors advocate treating these children with growth hormone replacement therapy because of the association between short stature and psychosocial morbidity.[74-76] However, several studies suggest that growth hormone treatment does not alleviate the psychosocial problems that accompany short stature or even that accompany a growth hormone deficiency specifically.[13,14,17]

Physicians should be very cautious in offering hope of catch-up growth to young patients who receive growth hormone replacement therapy, as one report noted

reactive depression in some children whose growth velocity did not improve or did not improve sufficiently to satisfy the child or the parents.[77] Clearly, physicians must be mindful of the danger of unrealistic expectations and must counsel accordingly.

This raises a very important point that is often overlooked in review articles: the treatment of the child or adolescent with short stature involves more than clinical investigation and therapeutic intervention aimed at correcting or reversing the short stature. Psychosocial correlates of short stature can affect the ultimate character, socio-economic status, and psychosocial well-being of the adult with short stature. Thus, the identification of psychosocial risk factors and appropriate intervention, if possible, can be a crucial aspect of care for some cases. This issue is addressed in Part 2 of this review (page 2217). ■

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